General

Guideline Title

American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy.

Bibliographic Source(s)

Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015 Jan;148(1):215-9. [4 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of evidence (high, moderate, low, very low) and strength of recommendation (strong, weak) are provided at the end of the "Major Recommendations" field.

1. Is antiviral prophylaxis needed for hepatitis B surface antigen (HBsAg)-positive patients who will undergo immunosuppressive drug therapy?
2. Is antiviral prophylaxis needed for HBsAg-negative, antibody to hepatitis B core antigen (anti-HBc)-positive patients who will undergo immunosuppressive drug therapy?
   The American Gastroenterological Association (AGA) recommends antiviral prophylaxis over no prophylaxis for patients at high risk undergoing immunosuppressive drug therapy. (Strong recommendation, Moderate-quality evidence)

   Comments: Treatment should be continued for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B cell-depleting agents).

   The AGA suggests antiviral prophylaxis over monitoring for patients at moderate risk undergoing immunosuppressive drug therapy. (Weak recommendation; Moderate-quality evidence)

   Comments: Treatment should be continued for 6 months after discontinuation of immunosuppressive therapy. Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg negative) may reasonably select no prophylaxis over antiviral prophylaxis.

The AGA suggests against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy who are at low risk for hepatitis B virus reactivation (HBVr). (Weak recommendation; Moderate-quality evidence)

3. Does the presence of antibody to hepatitis B surface antigen in addition to anti-HBc in HBsAg-negative patients confer additional protection against HBVr?
   The AGA suggests against using anti-HBs status to guide antiviral prophylaxis for all risk groups. (Weak recommendation; Very low-quality evidence)

4. Is prophylactic treatment with third-generation nucleos(t)ide analogues more effective than first- or second-generation nucleos(t)ide agents?
   The AGA suggests use of antiviral drugs with a high barrier to resistance over lamivudine for prophylaxis in patients undergoing immunosuppressive drug therapy. (Weak recommendation; Moderate-quality evidence)

   Comments: Given the geographic variability in cost of antiviral therapy, those patients who put a higher value on cost and a lower value on avoiding the potentially small risk of resistance development (particularly in those who have an undetectable viral load and who are expected to use antiviral prophylaxis for ≤6 months) may reasonably select the least expensive antiviral hepatitis B medication over more expensive antiviral drugs with a higher barrier to resistance.

5. Is HBV deoxyribonucleic acid (DNA) monitoring followed by on-demand antiviral therapy as effective as prophylactic antiviral therapy?
   The AGA makes no recommendation for a strategy of HBV DNA monitoring followed by rescue treatment as an alternative to antiviral prophylaxis. (No recommendation – knowledge gap)

6. Is treatment of established HBVr with third-generation nucleos(t)ide agents more effective than first- or second-generation drugs?
   The AGA recommends antiviral drugs with a high barrier to resistance over lamivudine for established HBVr in patients undergoing immunosuppressive drug therapy. (Strong recommendation; Moderate-quality evidence)

7. Should patients who will undergo long-term immunosuppressive drug therapy be screened for HBV before starting treatment?
   The AGA recommends screening for HBV (HBsAg and anti-HBc, followed by a sensitive HBV DNA test if positive) in patients at moderate or high risk who will undergo immunosuppressive drug therapy. (Strong recommendation; Moderate-quality evidence)

   The AGA suggests against routinely screening for HBV in patients who will undergo immunosuppressive drug therapy and are at low risk. (Weak recommendation; Moderate-quality evidence)

   Comments: Patients in populations with a baseline prevalence likely exceeding 2% for chronic HBV should be screened according to Centers for Disease Control and Prevention and U.S. Preventive Services Task Force (USPSTF) recommendations.

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Quality of Evidence

Quality Level	Definitions
High	The Committee is very confident that the true effect lies close to that of the estimate of the effect supporting the recommendation
Moderate	The Committee is moderately confident in the estimate of effect supporting the recommendation: the true effect is likely to be close to the estimate of effect, but there is a possibility it will be substantially different
Low	The Committee's confidence in the effect supporting the recommendations is limited: the true effect may be substantially different from the estimate of the effect
Very Low	The Committee has very little confidence in the effect estimate supporting the recommendation: the true effect is likely to be substantially different from the estimate of effect

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Strength of Recommendations

Implications of strong and conditional (weak) guideline recommendations

- Strong recommendations
  - Patients: Most people in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.

    - Clinicians: Most patients should receive the recommended course of action. Adherence to this recommendation according to guidelines could be used as a quality criterion or a performance indicator.
    - Policy makers: The recommendation can be adapted as a policy in most situations.
- Conditional (weak) recommendations
    - Patients: The majority of people in this situation would want the suggested course of action, but many would not. Decision aids are useful in helping patients make decisions consistent with their values and preferences.
    - Clinicians: Examine a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).
    - Policy makers: There is a need for substantial debate and involvement of stakeholders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hepatitis B virus reactivation (HBVr)

Note: The guideline does not address the issue of flares of chronic HBV infection over time, HBVr in coinfection with human immunodeficiency virus, and HBVr in solid organ transplantation or hematopoietic stem cell transplantation.

Guideline Category

Prevention

Treatment

Clinical Specialty

Gastroenterology

Infectious Diseases

Internal Medicine

Intended Users

Physicians

Guideline Objective(s)

To present the official recommendations on the prevention and treatment of hepatitis B virus reactivation (HBVr) during immunosuppressive therapy

Target Population

Patients with or at risk of hepatitis B virus reactivation (HBVr) during immunosuppressive drug therapy

Interventions and Practices Considered

1. Antiviral prophylaxis (moderate to high risk patients undergoing immunosuppressive drug therapy)
2. Use of antiviral drugs with a high barrier to resistance over lamivudine for prophylaxis or established hepatitis B virus reactivation (HBVr)
3. Screening for HBV (hepatitis B surface antigen [HBsAg] and hepatitis B core antigen [anti-HBc], followed by a sensitive HBV deoxyribonucleic acid [DNA] test if positive) in moderate to high risk patients

Note: The following interventions were considered but not recommended or no recommendation was made:

Antiviral prophylaxis for low risk patients undergoing immunosuppressive drug therapy
Using anti-HBs status to guide antiviral prophylaxis
HBV DNA monitoring followed by rescue treatment as an alternative to antiviral prophylaxis
Routinely screening for HBV in low risk patients

Major Outcomes Considered

- Frequency of reactivation
- Severe elevation of alanine transaminase (ALT) level
- Reactivation-related death

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search

An information specialist developed a literature search with input from the authors. All search results were imported using bibliographic management software for deâ€duplication and title and abstract screening. The following bibliographic databases were searched through the Ovid interface: EBM Reviews; Cochrane Central Register of Controlled Trials (July 2013); Cochrane Database of Systematic Reviews (July 2005 to July 2013); Health Technology Assessment (3rd quarter EMB); EMBASE 1980 to 2013 week 35; Ovid MEDLINE. The reviewers applied a search filter for systematic reviews, metaâ€analyses, and health technology assessments for the questions on the use of antiviral therapy.

The primary search was accessed in July to September of 2013 and included all articles up to 1998 that were using the search terms of hepatitis B, HBV reactivation, antiâ€HBc, rituximab, immunosuppressive therapy, cancer chemotherapy, biologic modifiers, antiviral prophylaxis, lamivudine, entecavir, telbivudine, and tenofovir (see Appendix 1 in the technical review for search strategy [see the "Availability of Companion Documents" field]). The initial search revealed 744 publications and their corresponding titles and abstracts. The authors discarded 606 publications by sequentially examining the titles and then abstracts, and if applicable, after full text articles were retrieved. Reasons for exclusion were inappropriate content such as relevance to solid organ transplantation or antiviral therapy in cohorts who were not taking immune suppressive drug therapy. The reviewers also excluded articles dealing with bone marrow transplantation or hematopoietic stem cell transplantation due to the greater awareness of reactivation risk status and treatment policy in both hepatitis B surface antigen (HBsAg)â€positive and hepatitis B core antigen (anti-HBc)â€positive patients. Case reports, abstracts or conference proceedings were not preferred and were only used when there was a marked paucity of data. The remaining 98 references were sorted according to whether they would provide useful information to assess the individual Patient Intervention Comparison Outcome (PICO) questions (see Appendix 2 in the technical review for trial flow diagram).

Major databases such as MEDLINE and conference reports were also searched by the authors for studies which addressed the baseline risk for hepatitis B virus reactivation (HBVr) and outcomes of interest in defined populations. Prevalence studies were not included in the final analysis of data if they did not provide reasonable evidence for consecutive case reporting, if baseline HBV deoxyribonucleic acid (DNA) data were unavailable, or if the study lacked definable criteria by which reactivation could be diagnosed. Editorials and letters were deselected as were all observational studies in which it was thought that the study design could lead to an unacceptable level of confounding either in the diagnosis of

reactivation or in the assessment of outcomes due to antiviral therapy.

Number of Source Documents

98 studies were included in the qualitative synthesis. There were 5 studies included in the quantitative synthesis (meta-analysis).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Quality of Evidence

Quality Level	Definitions
High	The Committee is very confident that the true effect lies close to that of the estimate of the effect supporting the recommendation
Moderate	The Committee is moderately confident in the estimate of effect supporting the recommendation: the true effect is likely to be close to the estimate of effect, but there is a possibility it will be substantially different
Low	The Committee's confidence in the effect supporting the recommendations is limited: the true effect may be substantially different from the estimate of the effect
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Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Literature Search

The authors systematically reviewed and partitioned the evidence for each outcome across studies, assessed the quality of evidence for each outcome, and then presented the evidence to answer each specific Patient Intervention Comparative Outcome (PICO) question. The quality of the evidence was classified into 4 Grading of Recommendations Assessment, Development and Evaluation (GRADE) categories: high, moderate, low and very low and a summary of the evidence was documented in GRADE evidence profiles using the GRADEpro software. According to GRADE criteria, evidence from randomized, controlled clinical trials (RCTs) would start at high quality but rated down in the presence of serious risk of bias, inconsistency or heterogeneity, indirectness, imprecision and potential publication bias. Evidence from observational studies would start at low quality but were eligible to be rated up in the presence of large effect size. Observational studies were considered to be primarily helpful in the determination of baseline risk for hepatitis B virus reactivation (HBVr) and providing additional information on patient outcomes.

Extraction of Data and Analytic Approach

Numerator and denominator for each critical and important outcome were extracted from each study using preâ€tested data extraction sheets listing acceptable definitions for outcomes such as HBVr, hepatitis, liver failure, liverâ€related mortality and chemotherapy interruptions. When possible, pooled risk ratio (RR) was calculated for each outcome using the Mantelâ€Haenszel random effect model in RevMan 5.2. Funnel plots were inspected for heterogeneity in addition to formal analysis of heterogeneity (chisquare, $p<0.1$) and residual heterogeneity that was not

explained by chance (Iâ€squared). The number of studies were insufficient to formally test for funnel plot asymmetry to detect possible publication bias. As relative effects of interventions usually are stable across differing baseline risks, the reviewers initially pooled the results of all RCTs using antiviral regimens vs. placebo from different populations and different antiviral regimens (see Figure 1 in the technical review [see the "Availability of Companion Documents" field]). As relative effects appeared similar and little or no heterogeneity across studies were seen, a decision was made to apply the pooled relative effects to typical baseline risks from different populations (those that were seen in the included RCTs, but also from clinical settings where baseline risks were not available directly from RCTs) to arrive at representative risk differences that would be most suitable to inform clinical guidance.

As well done cohort studies from wellâ€defined populations (e.g., cancer or rheumatic disease populations) may provide accurate estimates of baseline risks of HBV reactivation, and the risk of reactivation is markedly different based on the patient's baseline HBV serologies, a comprehensive review of those prevalence rates, mostly from observational studies, was performed. When pooled estimates of baseline risk were obtained from untreated control arms of RCTs in addition to wellâ€done cohort studies that enrolled consecutive, untreated patients, baseline risk was transformed to natural log proportions and pooled using the fixed effects inverse variance method in OpenMeta[analyst].

For more information on the study evaluation, refer to the technical review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the American Gastroenterological Association (AGA) Governing Board.

The guideline was developed using a process outlined in the technical review (see the "Availability of Companion Documents" field). Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it (see the "Rating Scheme for the Strength of the Recommendations" field). Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review.

Four members of the guideline panel, along with AGA support staff, met in person with the authors of the technical review on May 31, 2014. The information in the technical review was discussed in a systematic manner, facilitating subsequent creation of the guideline recommendations for or against each intervention. The strength of each recommendation was also rated as either strong or weak (i.e., conditional).

Formulation of Patient Intervention Comparative Outcome (PICO) Questions

PICO questions were devised by the authors and approved for further study by the AGA governing board in July of 2013. Each PICO question asks if an intervention affects patient outcomes in a positive or negative way and each independently required a careful and coordinated search of the medical literature as described above (see Table 1 in the technical review). The following clinical outcomes were considered critical or important for decision making: 1) Severity of hepatitis; 2) disease morbidity, 3) resource utilization including the need for hospitalization; 4) liver related mortality; and 3) interruption of cancer chemotherapy or other immunosuppressive drug treatment (see Table 1 in the technical review).

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Strength of Recommendations

Implications of strong and conditional (weak) guideline recommendations

- Strong recommendations
    - Patients: Most people in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.
    - Clinicians: Most patients should receive the recommended course of action. Adherence to this recommendation according to guidelines could be used as a quality criterion or a performance indicator.
    - Policy makers: The recommendation can be adapted as a policy in most situations.

- Conditional (weak) recommendations
  - Patients: The majority of people in this situation would want the suggested course of action, but many would not. Decision aids are useful in helping patients make decisions consistent with their values and preferences.
  - Clinicians: Examine a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).
  - Policy makers: There is a need for substantial debate and involvement of stakeholders.

Cost Analysis

Cost-effectiveness studies of hepatitis B virus (HBV) screening in patients with cancer have shown that screening is cost beneficial in patients with non-Hodgkin lymphoma slated to receive rituximab and may be cost effective in patients with breast cancer slated to receive adjuvant chemotherapy if HBV infection is prevalent. Furthermore, a cost-effectiveness study of HBV screening in the general population showed that screening is cost effective even when the prevalence of HBV infection is as low as 0.3%.

Refer to the technical review (see the "Availability of Companion Documents" field) for more information on cost-effectiveness.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the prevention and treatment of hepatitis B virus reactivation (HBVr) during immunosuppressive therapy. The guideline was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the AGA Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The benefits of screening for hepatitis B virus (HBV) before treatment with long-term immunosuppressive drug therapy include early identification of chronic HBV infection or resolved HBV infection in patients who will be treated with immunosuppressive therapy such that prophylaxis can be used, if appropriate, to minimize the risk of reactivation and associated morbidity and mortality.

Potential Harms

Deterrents to screening in the general population include the remote possibility of false-positive screening results and the potential emotional and financial impact of a new diagnosis of hepatitis B virus (HBV) infection.

Qualifying Statements

Qualifying Statements

Despite the large number of published studies, in most cases the Committee's recommendations are weak because either (1) the quality of the available data and/or the baseline risk of hepatitis B virus reactivation (HBVr) is low or uncertain and/or (2) the balance of risks and benefits for a particular strategy does not overwhelmingly support its use. However, there are moderately robust data to support a strong recommendation for the use of prophylaxis in those at high risk for HBVr. There is a large knowledge gap in making any recommendation on the strategy of monitoring HBV deoxyribonucleic acid (DNA) and intervening with a therapeutic regimen after diagnosing HBVr. There is a large knowledge gap in making any recommendation on the strategy of monitoring HBV DNA and intervening with a therapeutic regimen after diagnosing HBVr.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015 Jan;148(1):215-9. [4 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Jan

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Clinical Practice Guideline Committee

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Financial Disclosures/Conflicts of Interest

All members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Gastroenterology Journal Web site .

Print copies: Chair, Clinical Guideline Committee, AGA National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. E-mail: msiedler@gastro.org; telephone: (301) 941-2618.

Availability of Companion Documents

The following are available:

- American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy. Gastroenterology. 2015 Jan;148(1):221–244. Electronic copies: Available from the Gastroenterology Journal Web site .
- The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Electronic copies: Available to subscribers from the Clinical Gastroenterology and Hepatology Web site .
- AGA Institute guideline on hepatitis B reactivation (HBVr) clinical decision support tool. 2014. Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 27, 2015. The information was verified by the guideline developer on March 9, 2015.

Copyright Statement

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